REMARKS

Claim 1 has been amended to define m as being from 3 - 7 and new Claim 11 added defining m as 3, 5 or7. Grammatical corrections have been made in Claims 2, 5 and 6..

Support for the values on m set out in Claim 1 is found in the original specification on page 7 lines 10 - 14 disclosing the compounds of the general formula $C_{60}H_n[NH(CH_2)_mC(O)O]_n$, wherein "m" is 3, 5 and 7, namely fullerene-polyamino-butyric acid (m=3), fullerene-polyamino-caproic acid (m=5), and fullerene-polyamino-octanoic acid (m=7). The above compounds were not only synthesized and their physical-chemical properties characterized using IR-spectroscopy (see, e.g. Example 2, Fig. 1 to 4), ^{13}C-NMR and ^{1}H-NMR spectroscopy (see, e.g. p. 8-9), and TLC (see, e.g. p. 8, Example 3, Fig. 5), but the compounds were also tested for their biological activity *in vitro* (Examples 4 to 7) and used in the treatment of volunteer patients *in vivo* (Example 9).

It is therefore submitted that the invention s claimed meets the written description requirement of 35 USC 112 paragraph 1.

Turning to the rejection under 35 USC 103, the Examiner alleges that pending Claims 1, 3 to 4, and 11 to 12 are unpatentable (obvious) over Gan et al. (Chinese Chemical Letters, 1994, 5, 4, 275-278) in view of Chiang et al. (US 5,648,523).

The Examiner argues that in case of an alkyl chain "an extension by one carbon is expected to result in compounds with similar properties absent of unexpected results". The Applicant respectfully disagrees to the above allegation. Section 2144.09 of the Manual of Patent Examining Procedure makes the following points:

1. Rejection based on close structural similarity is founded on the expectation that compounds similar in structure will have similar properties;
2. Homology and isomerism are facts which must be considered with all other relevant facts in determining obviousness;
3. Presence of a true homologous or isomeric relationship is not controlling;
4. Presence or absence of prior art suggestion of method of making a claimed compound may be relevant in determining *prima facie* obviousness;
5. Presumption of obviousness based on structural similarity is overcome where there is no reasonable expectation of similar properties;
6. If prior art compounds have no utility, or utility only as intermediates, claimed structurally similar compounds may not be *prima facie* obvious over the prior art; and

Taking all of these points into consideration, it is submitted that no case of

prima facies obviousness has been made out.

The Applicant believes that the Examiner is oversimplifying in the statement noted above as to whether one skilled in the art would expect that extension of an alkyl chain would be expected to produce compounds of similar properties. In the present case, the properties in issue are biological properties. The issue is whether one skilled in the art would expect similarity in biological activity between the compounds of the prior art and those claimed. This requires prediction of the results of a much more complex interaction than was the case with simple chemical properties involved in the case law on which traditional views on the patentability of "homolgs" were based. As noted by the points set out in the MPEP noted above, a more sophisticated approach is now required. Interaction with a cognate biological target may be dramatically affected by a very subtle change in the chemical structure of the interacting moieties.

Furthermore, the Applicant draws the Examiner's attention to the fact that the only potential utility of the disclosed derivatives envisaged by Gan et al. consists in that they can serve as "good precursors for further derivatization study, such as complexation with metal ions especially rare earth metal ion". Gan et al. neither mentions nor even suggests that the specific fullerene derivative produced by the addition reaction of beta-alanine could be of any potential pharmaceutical relevance. The research paper merely mentions "the remarkable solubility of these derivatives in water". Therefore, if one were to follow the logic proposed by the Examiner the common properties shared by the compound disclosed in Gan et al. and the compounds of the instant invention should be

limited to their solubility in water only. A mere fact that certain compounds are water soluble and the statement that "the remarkable solubility of these derivatives in water makes them good precursors for further derivatization study, such as complexation with metal ions especially rare earth metal ion" (see Gan et al., p. 277, lines 4 and 5 from the bottom of the page) would not motivate a skilled person to assess these compounds for any biological/pharmacological activity, specifically for anti-viral activity.

The other prior art document mentioned by the Examiner, Chiang et al. (US 5,648,523) teaches an extremely broad group of fullerene derivatives which, however, does not encompass the water-soluble compounds of fullerene polycarboxylic anions of the instant invention characterized by the general formula $C_{60}H_n[NH(CH_2)_mC(O)O]_n$. The prior art compounds are asserted to be scavengers of free radicals.

It is submitted that the mere fact that certain fullerene derivatives capable of scavenging free radicals could be formulated into pharmaceutical compositions would not motivate one of ordinary skill in the art to formulate any other fullerene derivative into a pharmaceutical composition (no matter what the particular dosage form is – a tablet, a capsule, a suppository or a solution for injections) in the absence of any information or suggestion whatsoever implying that such fullerene derivative could have some pharmacologically relevant activity.

The Supreme Court has pointed out that:

> [R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR International Co. v. Teleflex, Inc.* 550 U.S. 398 82 USPQ2d 1385 (2007) .

As discussed above, no such rational underpinning exists for producing the modifying the teaching of the prior art to produce the compounds of the present invention.

The Applicant respectfully submits that neither considered alone nor taken in combination the prior art documents Gan et al. and Chiang et al. could compromise non-obviousness of the inventions according to Claims 1, 3 to 4, and 11 to 12. The Applicant respectfully requests the Examiner to withdraw the above rejection.

The Examiner further alleges that pending Claims 2 and 5 to 6 are unpatentable (obvious) over Gan et al. (Chinese Chemical Letters, 1994, 5, 4, 275-278) in view of Miller et al. (RU 2196602).

The Applicant is pleased to note that the Examiner is accurately quoting the peculiarities of a method disclosed in Miller et al. Indeed, according to the method disclosed in Miller et al. a reaction between fullerene (added to a reaction mixture as a solution in o-dichlorobenzene) and an amino acid sodium or potassium salt (added as an aqueous solution) is carried out in a two-phase mixed solvent system comprising water and

dichlorobenzene at 60 °C for 6-8 hours under stirring. The method is specifically intended to produce a product of mono-addition of an amino acid (specifically, aminocaproic or aminobutyric) to fullerene. What is extremely important is that the relative amounts of fullerene and amino acid that are brought into reaction are not specified. Furthermore, Miller et al. neither discloses nor even suggests that the reaction conditions that are suitable for producing the product of mono-addition of an amino acid or a dipeptide to fullerene could be employed to carry out a reaction of poly-addition of an amino acid to fullerene. Let alone the fact (see below) that the reaction conditions employed by Miller at al. are clearly distinct from those specified in pending Claim 2.

On the other hand, the method of Claim 2 of the instant invention is specifically intended to produce a product of poly-addition of 2 to 12 amino acid molecules to the fullerene core and is carried out in an one-phase solvent system that is free from aqueous phase. Furthermore, a solubilizer selected from a specific group of compounds is added to the reaction mixture. As the solubilizer use is made of various polyethylene oxides: polyethylene glycols with a molecular weight of from 150 to 400 and higher and also dimethyl ethers of polyethylene or 18-crown-6.

The Applicant respectfully submits that if considered alone, Miller et al. would not motivate a skilled person to employ the reaction conditions specifically intended to yield a product of mono-addition of an amino acid to fullerene to produce a novel fullerene compound that results from the reaction of poly-addition of amino-acid

molecules to fullerene. All the more so since the actual conditions as recited in Claim 2 of the present invention are clearly distinct from those disclosed in Miller et al. Similarly, a skilled person would not be motivated to combine the disclosure of Gan et al. with certain features of the method disclosed in Miller et al. to arrive to a technical solution provided by the instant invention, namely to a method for the production of a novel water-soluble compound of fullerene polycarboxylic anions. None of the prior art documents Gan et al. and Miller et al. disclosed or even suggested that the specific reaction conditions including a one-phase non-aqueous solvent system and selection of a specific solubilizer could be used to produce a novel compound of the present invention which is a product of poly-addition of 2 to 12 amino acid molecules to the fullerene core.

As concerns the Examiner's allegation that "similar compounds are expected to possess similar characteristics and/or properties" the Applicant respectfully draws the Examiner's attention to the following facts. It appears that the Examiner is regarding the compounds disclosed in Chiang et al. (see above) as related to the compounds of the present invention. The compounds disclosed in Chiang et al. exhibit an activity of free radical scavengers. Fullerene derivatives containing a single covalently linked amino acid residue disclosed in Miller et al. do exhibit an anti-viral activity against HIV and CMV. A fullerene derivative disclosed in Gan et al. has not been reported to have any relevant biological-pharmacological activity. The mere fact that the product of mono-addition of an amino acid to fullerene disclosed in Miller et al. exhibits certain anti-viral activity could not serve for a skilled person as a hint that the same activity could be

expected for compounds belonging to an absolutely structurally distinct group of fullerene derivatives disclosed in the present application, namely the products of poly-addition of amino acids to fullerene. Let alone the fact that the latter could have been well devoid of any activity at all.

Furthermore, Miller et al. is silent about potential *in-vivo* anti-viral effect of the compounds disclosed therein in respect of viruses belonging to the family *Herpesviridae* other than CMV, or viruses belonging to other families of membrane (enveloped) viruses such as, e.g. HCV belonging to a distinct family *Flaviviridae*.

The Applicant respectfully submits that neither considered alone nor taken in combination the prior art documents Gan et al. and Miller et al. could compromise non-obviousness of the inventions according to Claims 2 and 5 to 6 and that the requirements of 35 USC 103 are met for these claims also.

It is noted that no rejection under 35 USC 103 has bee made against any of Claims 7 -10 directed to compounds wherein m is defined as 5 (Claims 7 and 10) or n has values of 4 to 6 or 6 (Claims 8 - 10). Possibly therefore, the examiner accepts either that there is no prima facie case of obviousness against these compounds or that the dtat set out in the application overcomes any such case. As noted above, the applicants do not believe that there is any *prima facies* case of obviousness against any of the claims. If, however, the Examiner's views on Claim 7 - 10 are based on the data set out in the application, it is

pointed out that although tables 2, 3, 5, 7.1, 7.2, 11,12. 12 and 14 all set out results of compounds wherein m is 5 and demonstrate the surprising anti-viral properties thereof, tables 8, 9 and 10 provide information on compounds wherein m is 3 and 7. These tables show substantial efficacy for these compounds against HIV-1 and HSV-1 which, even if there were any prima facie case of obviousness, which as explained above is denied, such a case is rebutted by these data.

In view of the foregoing, it is submitted that this application is in order for allowance and an early action to this end is respectfully solicited.

Respectfully submitted,

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